REMARKS

Claims 1-18 are under examination in the application. Claims 1-18 have been amended above. Support for the amendments can be found throughout the specification. Specifically, support for "integrin $\alpha_v\beta_3$ binding activity, integrin $\alpha_v\beta_3$ binding specificity or integrin $\alpha_v\beta_3$-inhibitory activity" can be found, for example, on page 14, lines 4-10. Support for "CDR-grafted" can be found, for example, on page 8, line 15, to page 10, line 10. Accordingly, these amendments do not raise an issue of new matter and entry thereof is respectfully requested.

Claims 1-18 stand provisionally rejected under the judicially created doctrine of obviousness type double patenting as allegedly unpatentable over claims 1-48 of copending application serial No. 08/790,540, which Applicant assumes should be copending application serial No. 08/791,391. Applicant respectfully requests that this provisional ground of rejection be deferred until there is an indication of allowable subject matter.

Claims 1-18 are alleged to be directed to an invention not patentably distinct from claims 1-18 of commonly assigned application serial No. 08/790,540, which Applicant assumes should be commonly assigned U.S. application serial No. 08/791,391. The Office Action states that the assignee is required under 37 C.F.R. § 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in the instant application was made or to name the prior inventor of the

conflicting subject matter. Applicant respectfully requests that this requirement be held in abeyance until there is an indication of allowable subject matter.

The present invention provides LM609 CDR-grafted antibody, which is a non-mouse antibody or functional fragment thereof that contains heavy and light chain CDR amino acid sequences derived from LM609 and has integrin $\alpha_v\beta_3$ binding activity, integrin $\alpha_v\beta_3$ binding specificity or integrin $\alpha_v\beta_3$-inhibitory activity. Nucleic acids encoding LM609 CDR-grafted antibody heavy and light chains are additionally provided. Applicant has reviewed the Office Action and respectfully traverses all grounds for rejecting the claims for the reasons that follow.

REJECTIONS UNDER 35 U.S.C. § 112

Claims 1-18 stand rejected under 35 U.S.C. § 112, first and second paragraphs, as allegedly lacking enablement and as allegedly indefinite for use of the terms "substantially the same" and "functional fragments thereof." The Office Action alleges that Applicant acknowledges that such phrases or terms encompass a considerable degree of modifications. The Office Action further alleges that these terms are ambiguous and unclear in the context of the claimed limitation versus Applicant's asserted limitations of binding specificity and inhibitory activity. The Office Action states that the metes and bounds of the terms are unclear in the absence of a clear recitation of specificity and function.

Applicant maintains that the terms "substantially the same" and "functional fragment thereof" are clear to one skilled in the art in view of the specification. The specification teaches that a nucleotide or amino acid sequence that is "substantially the same" shows a considerable degree, amount or extent of sequence identity when compared to a reference sequence (page 12, line 18, to page 13, line 16). A nucleotide sequence which is substantially the same as a heavy or light chain of LM609 or a LM609 grafted antibody is a sequence which exhibits characteristics that are recognizable as encoding the amino acid sequence of LM609 or a LM609 grafted antibody, including minor modifications. Similarly, an amino acid sequence which is substantially the same amino acid sequence as a heavy or light chain of a LM609 grafted antibody, or functional fragment thereof, is a sequence which exhibits characteristics that are definitively known or recognizable as representing the amino acid sequence of a LM609 grafted antibody, including minor modifications. Therefore, Applicant submits that the meaning of the term "substantially the same" is clear and definite.

Although Applicant believes that the term "selective binding affinity to $\alpha_v\beta_3$" is descriptive of the claimed LM609 CDR-grafted antibody, Applicant has nevertheless amended claim 1 to indicate that LM609 CDR-grafted antibody or functional fragments thereof have integrin $\alpha_v\beta_3$ binding activity, integrin $\alpha_v\beta_3$ binding specificity or integrin $\alpha_v\beta_3$-inhibitory activity. Therefore, Applicant submits that the amended claims recite structural and functional characteristics of LM609 CDR-grafted

antibody and that the meaning of the term "substantially the same" is clear and definite.

The specification further teaches that a "functional fragment" of LM609 grafted antibody is a portion of a LM609 grafted antibody, including heavy or light chain polypeptides, "which still retains some or all of the $\alpha_v\beta_3$ binding activity, $\alpha_v\beta_3$ binding specificity and/or integrin $\alpha_v\beta_3$-inhibitory activity" (page 14, lines 4-23). Although Applicant submits that the term "functional fragment" is clear in view of the specification, claim 1 has been amended to indicate that the LM609 CDR-grafted antibody has integrin $\alpha_v\beta_3$ binding activity, integrin $\alpha_v\beta_3$ binding specificity or integrin $\alpha_v\beta_3$-inhibitory activity. Therefore, Applicant submits that the meaning of the terms "substantially the same" and "functional fragment thereof" is clear and definite.

Applicant respectfully disagrees with the Examiner's assertions and reemphasize that the terms "substantially the same" and "functional fragments thereof" do not encompass a considerable degree of modifications but, rather, a considerable degree, amount or extent of sequence identity when compared to a reference sequence, including minor modifications that allow a LM609 CDR-grafted antibody to retain integrin $\alpha_v\beta_3$ binding activity, integrin $\alpha_v\beta_3$ binding specificity or integrin $\alpha_v\beta_3$-inhibitory activity. The specification sets forth the modifications encompassed by the terms "substantially the same" and "functional fragment thereof" in regard to a LM609 CDR-grafted antibody. The specification teaches, for example,

that minor modifications of the nucleotide sequences are included as heavy and light chain LM609 grafted antibody encoding nucleic acids and their functional fragments (page 17, line 21, to page 18, line 11, and page 18, lines 24-29). Minor modifications include changes in nucleotide sequence that do not change the encoded amino acid sequence due to degeneracy in the genetic code and changes that result in conservative amino acid substitutions without destroying integrin $\alpha_v\beta_3$ binding activity, integrin $\alpha_v\beta_3$ binding specificity or integrin $\alpha_v\beta_3$-inhibitory activity.

Minor modifications resulting in substantially the same sequence also include changes that allow for the functional replacement of amino acids by identifying the amino acids that are desired to be changed, incorporating the changes into the encoding nucleic acid and then determining the function of the recombinantly expressed and modified LM609 CDR-grafted antibody polypeptide by screening for LM609 CDR-grafted antibody polypeptides that retain function (page 18, line 24, to page 19, line 16). Therefore, an amino acid sequence or nucleic acid encoding an amino acid sequence that incorporates minor modifications is "substantially the same" as LM609 grafted antibody if it exhibits characteristics that are recognizable as representing the sequence of LM609 grafted antibody, including $\alpha_v\beta_3$ binding activity, $\alpha_v\beta_3$ binding specificity or integrin $\alpha_v\beta_3$ inhibitory activity (page 13, lines 1-16 and page 14, lines 4-10).

In light of the above remarks, Applicant submits that claims directed to a LM609 CDR-grafted antibody recite structural

and functional characteristics of the antibody and, together with the teachings of the specification, provide sufficient guidance to enable one skilled in the art to practice the invention as claimed. Furthermore, Applicant maintains that the terms "substantially the same" and "functional fragment thereof" are clear and definite. Therefore, the rejection of claims 1-18 under 35 U.S.C. § 112, first and second paragraphs, as allegedly lacking enablement and as allegedly vague and indefinite is respectfully requested to be withdrawn.

Claims 1-18 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for use of the term "grafted." Applicant maintains that this term is clear and descriptive to those skilled in the art. However, claims 1-18 have been amended above to conform to the language suggested by the Examiner. Therefore, in view of the amendment to LM609 "CDR-grafted" antibody, the rejection of these claims as allegedly indefinite is moot and is respectfully requested to be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 102

An issue of public use or on sale activity has been raised under 35 U.S.C. § 102(b). The Office Action states that articles in Biotechnology Newswatch, dated January 16, 1995, and February 6, 1995, disclose the use of LM609 antibody including the humanized version of the antibody.

Applicant submits that the claimed LM609 CDR-grafted antibody was not in public use or on sale in this country more than one year prior to the filing date of the above-identified application. As evidence that the description within the Biotechnology Newswatch articles does not establish public use or on sale activity of the claimed antibodies, Applicant submits herewith a Declaration under 37 C.F.R. § 1.132 (Exhibit 1) attesting that an agreement was reached between Ixsys and Celltech Biologics, which is recited in the Biotechnology Newswatch article dated February 6, 1995, for Celltech Biologics to construct mammalian expression vectors and mammalian cell lines expressing antibody generated using nucleic acid provided by Ixsys and to produce the antibody. The Declaration and accompanying Exhibit A provide evidence that Ixsys maintained control of the use of any LM609 grafted antibody.

The Declaration indicates that, in interactions with third parties, Ixsys maintained control of all antibody materials, including any LM609 grafted antibody, any nucleic acid encoding LM609 grafted antibody, any cell lines containing nucleic acid encoding LM609 grafted antibody, and any related materials or information. Attached as Exhibit A are portions of an agreement with Celltech Therapeutics and its affiliate Celltech Biologics, which has been redacted to remove dates and unrelated information. The Declaration and accompanying Exhibit A indicate that Celltech Biologics was under obligation to use the Customer materials, which include nucleic acid provided by Ixsys, cell lines containing the nucleic acid, and information provided by Ixsys, or any part thereof, only for the

purpose of the agreement. Celltech Biologics was under obligation to maintain the confidentiality of nucleic acid provided by Ixsys, the cell lines containing the nucleic acid and the antibody product. Thus, the use of any LM609 grafted antibody by Celltech Biologics was under the control of Ixsys. The Declaration concludes that Ixsys maintained control of LM609 grafted antibody during any involvement with Celltech Biologics. The Declaration further concludes that LM609 grafted antibody was not on sale or in public use more than one year prior to January 30, 1997. In regard to the reference to Vitaxin in the Biotechnology Newswatch article dated February 6, 1995, Applicant respectfully submits that Vitaxin is not claimed.

In regard to the assertion in the Office Action that the information in the Biotechnology Newswatch articles was sufficiently informing to the public of humanizing the LM609 antibody encompassed by the claimed invention, Applicant respectfully submits that public knowledge is not public use and is not anticipatory under 35 U.S.C. § 102(b). *TP Labs, Inc., v. Professional Positioners, Inc.*, 220 USPQ 577, 581 (Fed. Cir. 1984).

In light of the above remarks and attached Declaration and Exhibit A, Applicant maintains that LM609 grafted antibody was neither on sale or in public use in this country more than one year prior to the filing date of the above-identified application and respectfully request that this rejection be withdrawn.

In regard to the issue of inventorship, Applicant maintains that inventorship has been reviewed and determined to be correct. At most, Dr. Cheresh could be considered a collaborator but not an inventor of the claimed invention.

Claims 1 and 15-18 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Brooks et al., Cell 79:1157-1164 (1994). The Office Action alleges that the specification and Applicant's previously filed arguments indicate that "substantially the same" encompasses LM609 or LM609 grafted antibody and that the breadth of the claims reciting "substantially the same" variable region sequences reads on the LM609 antibody described by Brooks et al.

Applicant maintains that the claimed compositions directed to a LM609 grafted antibody are novel over Brooks et al. Brooks et al. appears to describe inhibition of angiogenesis by the mouse monoclonal antibody LM609. In contrast, Applicant's claimed antibodies have human acceptor framework sequences with LM609 CDRs and, therefore, are non-mouse antibodies (page 8, line 15, to page 9, line 16). As described in Example II, the claimed antibodies were generated by inserting LM609 CDR nucleic acid sequences into human framework variable region sequences, human heavy chain variable region M72 'CL and human light chain variable region LS1 'CL. Although portions of the claimed antibodies, specifically the heavy and light chain CDRs, are found in LM609, Brooks et al. does not teach or suggest the claimed human acceptor framework sequences with LM609 CDRs corresponding to SEQ ID NOS:2 and 32 for LM609 CDR-grafted

antibody. Therefore, Brooks et al. does not teach or suggest the claimed non-mouse antibodies or any of the structural characteristics of the antibodies, which are recited in the claims.

In regard to the breadth of claims reciting substantially the same, Applicant respectfully submits that, as described in the specification, for example, on page 12, line 18, to page 13, line 16, an amino acid sequence which is substantially the same amino acid sequence as a heavy or light chain of a LM609 grafted antibody refers to a sequence which exhibits characteristics that are definitively known or recognizable as representing the amino acid sequence of a LM609 grafted antibody, not LM609. Such recognizable characteristics include structural and functional characteristics, both of which are recited in the claims.

In contrast to the claims, which are directed to a LM609 CDR-grafted antibody and recite structural characteristics of the antibody, Brooks et al. does not teach or suggest any of the recited structural characteristics of a LM609 CDR-grafted antibody. Specifically, Brooks et al. does not teach or suggest an amino acid sequence or a sequence that is substantially the same amino acid sequence as that corresponding to a LM609 CDR-grafted antibody. Furthermore, Brooks et al. does not teach or suggest the claimed human acceptor framework sequences with LM609 CDRs corresponding to SEQ ID NOS:2 and 32 for LM609 CDR-grafted antibody. Absent any teaching or suggestion of the claimed non-mouse antibody or the sequences specifically recited

in the claims, Brooks et al. does not disclose each and every facet of the claimed invention and, therefore, cannot anticipate the invention as claimed. Accordingly, Applicant respectfully requests that this ground for rejection be withdrawn.

Claims 1 and 15-18 also stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Choi et al., J. Vascular Surg. 19:125-134 (1994). The Office Action alleges that the breadth of the claims reciting "substantially the same" variable region sequences reads on the LM609 antibody described by Choi et al.

Applicant maintains that the claimed compositions directed to a LM609 grafted antibody are novel over Choi et al. Choi et al. appears to describe inhibition of PDGF-mediated human smooth muscle cell migration by the mouse monoclonal antibody LM609. In contrast, Applicant's claimed antibodies have human acceptor framework sequences with LM609 CDRs and, therefore, are non-mouse antibodies (page 8, line 15, to page 9, line 16). Although the claimed antibodies contain the heavy and light chain CDRs of LM609, Choi et al. does not teach or suggest the claimed human acceptor framework sequences with LM609 CDRs corresponding to SEQ ID NOS:2 and 32 for LM609 CDR-grafted antibody. Therefore, Choi et al. does not teach or suggest the claimed non-mouse antibodies or any structural characteristics of the antibodies, which are recited in the claims.

In regard to the breadth of claims reciting substantially the same, Applicant respectfully submits that, as

described in the specification, for example, on page 12, line 18, to page 13, line 16, an amino acid sequence which is substantially the same amino acid sequence as a heavy or light chain of a LM609 grafted antibody refers to a sequence which exhibits characteristics that are definitively known or recognizable as representing the amino acid sequence of a LM609 grafted antibody, not LM609. Such recognizable characteristics include structural and functional characteristics, both of which are recited in the claims.

In contrast to the claims, which are directed to a LM609 CDR-grafted antibody and recite structural characteristics of the antibody, Choi et al. does not teach or suggest any of the recited structural characteristics of LM609 CDR-grafted antibody. Specifically, Choi et al. does not teach or suggest an amino acid sequence or a sequence that is substantially the same amino acid sequence as that corresponding to a LM609 CDR-grafted antibody. Furthermore, Choi et al. does not teach or suggest the claimed human acceptor framework sequences with LM609 CDRs corresponding to SEQ ID NOS:2 and 32 for LM609 CDR-grafted antibody. Absent any teaching or suggestion of the claimed non-mouse antibody or the sequences specifically recited in the claims, Choi et al. does not disclose each and every facet of the claimed invention and, therefore, cannot anticipate the invention as claimed. Accordingly, Applicant respectfully requests that this ground for rejection be withdrawn.

Claims 1 and 15-18 stand rejected under 35 U.S.C. 102(a)(e) as allegedly anticipated by Kim et al., U.S. Patent No.

5,578,704. The Office Action alleges that the breadth of the claims reciting "substantially the same" variable region sequences reads on the LM609 antibody described by Kim et al.

Applicant maintains that the claimed compositions directed to a LM609 grafted antibody are novel over Kim et al. Kim et al. appears to describe hybridomas and murine monoclonal antibodies that specifically bind to $\alpha_V\beta_3$ integrin on human osteoclasts and describes the previously published mouse monoclonal antibody LM609. In contrast, Applicant's claimed antibodies have human acceptor framework sequences with LM609 CDRs and, therefore, are non-mouse antibodies (page 8, line 15, to page 9, line 16). Although the claimed antibodies contain the heavy and light chain CDRs of LM609, Kim et al. does not teach or suggest the claimed human acceptor framework sequences with LM609 CDRs corresponding to SEQ ID NOS:2 and 32 for LM609 CDR-grafted antibody. Therefore, Kim et al. does not teach or suggest the claimed non-mouse antibodies or any of the structural characteristics of the antibodies, which are recited in the claims.

In regard to the breadth of claims reciting substantially the same, Applicant respectfully submits that, as described in the specification, for example, on page 12, line 18, to page 13, line 16, an amino acid sequence which is substantially the same amino acid sequence as a heavy or light chain of a LM609 grafted antibody refers to a sequence which exhibits characteristics that are definitively known or recognizable as representing the amino acid sequence of a LM609

grafted antibody, not LM609. Such recognizable characteristics include structural and functional characteristics, both of which are recited in the claims.

In contrast to the claims, which are directed to a LM609 CDR-grafted antibody and recite structural characteristics of the antibody, Kim et al. does not teach or suggest any of the recited structural characteristics of a LM609 CDR-grafted antibody. Specifically, Kim et al. does not teach or suggest an amino acid sequence or a sequence that is substantially the same amino acid sequence as that corresponding to a LM609 CDR-grafted antibody. Furthermore, Kim et al. does not teach or suggest the claimed human acceptor framework sequences with LM609 CDRs corresponding to SEQ ID NOS:2 and 32 for LM609 CDR-grafted antibody. Absent any teaching or suggestion of the claimed non-mouse antibody or the sequences specifically recited in the claims, Kim et al. does not disclose each and every facet of the claimed invention and, therefore, cannot anticipate the invention as claimed. Accordingly, Applicant respectfully requests that this ground for rejection be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 103

Claims 1-18 stand rejected under 35 U.S.C. § 103 as allegedly unpatentable over Brooks et al., *supra*, Choi et al., *supra*, or Kim et al., *supra*, in view of the known art related to gene cloning and expression strategies for deriving recombinant antibodies and fragments thereof. The Office Action states that the proposition that the references failed to teach the structure

of the claimed antibody and precludes the teachings thereof from serving as evidence to establish a *prima facie* case of obviousness is contrary to a body of law which holds that a product may be described by the process of making it. The Office Action cites *Ex parte Goldgaber*, 41 USPQ2d 1173, 1176 (Board Patent Appeals Inter.), as indicating that nothing is intrinsically wrong in the application of methodology in the rejection of product claims under 35 U.S.C. § 103 depending on the particular facts of the case, the manner and context in which methodology applies and the overall logic of the rejection. The Office Action further states that *Bell* and *Deuel* do not issue a blanket prohibition against the application of methodology in rejecting a product claimed defining DNA and that it is perfectly acceptable to consider the method by which a compound is made in evaluating the obviousness of the compound.

The Office Action states that it would have been a matter of routine experimentation to generate chimeric or humanized LM609 antibodies and DNA encoding the antibodies given the LM609 antibody and hybridoma and its associated properties known in the art. Although the cited references are alleged to describe $\alpha_v\beta_3$-specific antibodies and LM609 specificity and associated properties as valuable diagnostic and therapeutic tools in various biological processes, the Office Action acknowledges that these references differ from the claims by not disclosing the generation of recombinant forms and nucleic acids of the LM609 antibody and hybridoma.

The Office Action concludes that no objective evidence has been provided to indicate that the resulting amino acid or nucleotide sequences were unobvious at the time the invention was made. The Office Action alleges that the breadth of the claims reciting "substantially the same" variable region sequences reads on a genus of antibodies and nucleic acids encompassed by LM609 antibody and modifications thereof.

Applicant respectfully maintains that the claimed compositions directed to LM609 grafted antibody and encoding nucleic acids and LM609 encoding nucleic acids are novel and unobvious over the cited references. The claims recite structural characteristics of LM609 CDR-grafted antibody and encoding nucleic acids by reciting specific SEQ ID NOS for each of the claimed antibodies or nucleic acids.

In regard to the application of methodology to composition claims in view of *Bell* and *Deuel*, Applicant respectfully submits that, in order to render a claim obvious, the prior art should provide teachings directed to the claimed composition. "A general motivation to search for some gene that exists does not necessarily make obvious a specifically-defined gene that is subsequently obtained as a result of that search." "We today reaffirm the principle, stated in *Bell*, that the existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the claimed DNAs." *In re Deuel*, 34 USPQ 2d 1215 (Fed. Cir. 1995). "Because Deuel claims new

chemical entities in structural terms, a *prima facie* case of unpatentability requires that the teachings of the prior art suggest *the claimed compounds* to a person of ordinary skill in the art." *In re Deuel*, 34 USPQ 2d 1214 (Fed. Cir. 1995).

In contrast to the claims, which recite specific structural features of the claimed compositions, Brooks et al., Choi et al., and Kim et al. do not teach or suggest any structural characteristics of a LM609 CDR-grafted antibody or any structural characteristics of a nucleic acid encoding a LM609 CDR-grafted antibody. Specifically, the cited references do not teach or suggest any nucleotide or amino acid sequences corresponding to the variable regions of a LM609 CDR-grafted antibody. Absent the teachings of any nucleotide or amino acid sequences corresponding to a LM609 CDR-grafted antibody in the cited references, Applicant respectfully submits that the cited references do not render obvious the claims reciting specific SEQ ID NOS.

Furthermore, in each of *Bell*, *Deuel* and *Goldgaber*, the references cited for obviousness also described structural characteristics in that the amino acid sequence of at least a portion of the protein encoding the claimed nucleic acids was described. Therefore, each of the references cited for obviousness disclosed some structural information of the amino acids encoding the claimed nucleic acids. In contrast, neither Brooks et al., Choi et al. nor Kim et al. describe any structural features of the nucleotide or amino acid sequence of a LM609 CDR-grafted antibody. Moreover, absent any teachings in the

cited references of any structural characteristics of a nucleotide or amino acid sequence of a LM609 CDR-grafted antibody, Applicant respectfully submits that one skilled in the art would have been unable to obtain or predict any of the claimed sequences or minor modifications thereof in view of any of any of the cited references without obtaining the sequence of the LM609 variable regions, as was done by Applicant. Therefore, none of the claimed compositions directed to specifically recited nucleotide or amino acid sequences or substantially the same sequences would have been obvious in view of the cited references. Accordingly, the rejection of claims 1-18 as allegedly obvious is respectfully requested to be withdrawn.

CONCLUSION

In light of the amendments and remarks herein, Applicant submits that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call Cathryn Campbell or the undersigned agent if there are any questions.

Respectfully submitted,

Date: December 9, 1998

Andrea L. Gashler

Andrea L. Gashler
Registration No. 41,029
Telephone No.: (619) 535-9001
Facsimile No.: (619) 535-8949

CAMPBELL & FLORES LLP
4370 La Jolla Village Drive
Suite 700
San Diego, California 92122

PATENT
Our Docket: P-IX 2405

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: William D. Huse	Group Art Unit: 1642
Serial No.: 08/790,540	Examiner: P. Gambel
Filed: January 30, 1997	
For: ANTI-$\alpha_v\beta_3$ RECOMBINANT HUMAN ANTIBODIES, NUCLEIC ACIDS ENCODING SAME AND METHODS OF USE	

Asst. Commissioner for Patents
Washington, D.C. 20231

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

Sir:

I, William D. Huse, declare as follows:

1) I am the William D. Huse who is named as an inventor on the above-identified patent application.

2) I understand that the claims of the subject application stand rejected, in part, because the claimed LM609 CDR-grafted antibody is alleged to have been on sale or in public use more than one year prior to the filing of the above-identified application.

3) I conceived the idea of humanizing $\alpha_v\beta_3$ inhibitory antibodies. An agreement was reached with Scripps Research Institute, La Jolla, CA, to obtain the hybridoma producing the mouse LM609 antibody. The LM609 hybridoma was brought to Ixsys, Inc., where I, or those under my supervision, cloned the LM609 heavy and light chain variable region cDNA. LM609 grafted

antibodies were generated and developed having $\alpha_v\beta_3$ inhibitory activity.

4) Agreements made with third parties were confidential, and Ixsys maintained control of all antibody materials, including any LM609 grafted antibody, any nucleic acid encoding LM609 grafted antibody, any cell lines containing nucleic acid encoding LM609 grafted antibody, and any related materials or information. As evidence that Ixsys maintained control and confidentiality of these materials in agreements with third parties, attached herewith as Exhibit A are portions of an agreement with Celltech Therapeutics Limited and its affiliate, Celltech Biologics PLC. The agreement directed Celltech Biologics to construct mammalian expression vectors and mammalian cell lines expressing antibody generated using nucleic acid provided by Ixsys and to produce the antibody. As evidenced by Exhibit A, Celltech Biologics was under obligation to use the Customer Materials, cell lines containing Customer Materials and the Customer Information, or any part thereof, only for the purpose of the agreement. Celltech Biologics was under obligation to keep the Customer Materials, which included any nucleic acid provided by Ixsys, secure and safe from loss, was obligated not to part with the Customer Materials or antibody product except for the purposes of testing, and was obligated to maintain confidentiality and to ensure that any testing laboratories were similarly under an obligation to maintain confidentiality of the materials and products (Exhibit A, Section 2.3).

5) At all times during any involvement with Celltech Biologics, Ixsys maintained control of LM609 grafted antibody, related materials and their use. LM609 grafted antibody was not on sale or in public use more than one year prior to January 30, 1997.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that any such willful false statement may jeopardize the validity of the application or any patent issued thereon.

12/8/98
Date

WD
William D. Huse

THIS AGREEMENT is made the day of

BETWEEN Ixsys Inc of 3550 Dunhill Street, San Diego, CA 92121, USA (hereinafter referred to as "Ixsys" or the "Customer")

AND Celltech Therapeutics Limited of 216 Bath Road, Slough, Berkshire SL1 4EN, England (hereinafter referred to as "Celltech")

WHEREAS

A. Celltech has expertise in the construction of mammalian cell lines using recombinant DNA technology and the development of manufacturing processes using such cell lines and owns certain intellectual property rights in relation thereto; and

B. The Customer has cDNA coding for variable domains of a CDR grafted monoclonal antibody to vitronectin receptor known as huLM609 Product (as hereinafter defined); and

C. The Customer has requested Celltech to carry out a programme of research to construct mammalian cell lines using cDNA supplied by the Customer and to develop a manufacturing Process for Product; and

D. Celltech has appointed Celltech Biologics plc (Affiliate of Celltech) to act as its agent for the purposes of administering this Agreement as set forth herein and all communications and financial dealings with regard to this Agreement shall be between the Customer and Celltech Biologics plc in accordance with the provisions set out herein.

NOW THEREFORE it is hereby agreed by and between the parties as follows:

1. In this Agreement, its recitals and Schedules hereto, words and phrases defined in the Standard Terms for Contract Services set out in Schedule 4 hereto shall have the meanings set out therein.

2. Subject to the Standard Terms for Contract Services set out in Schedule 4 hereto Celltech agrees to carry out the Services and the Customer agrees to pay the Price together with any additional pre approved costs and expenses that fall due hereunder.

3. Any notice or other communication to be given under this Agreement shall be delivered personally or sent by first class pre-paid post or facsimile transmission addressed as follows:

If to the Customer to:	Ixsys Inc 3550 Dunhill Street San Diego CA 92121 USA
For the attention of:	Vice President of Business Development
Copy to:	Vice President of Pre Clinical Development
Facsimile:	619 597 4950
If to Celltech to:	Celltech Biologics plc 216 Bath Road Slough Berkshire SL1 4EN England
For the attention of:	Chief Executive
Copy for the attention of:	Contract Manager
Facsimile:	0753 536632

or to such other destination as either party hereto may hereafter notify to the other in accordance with the provisions of this clause. All other such notices or other communications shall be deemed to have been served as follows:

3.1 if delivered personally, at the time of such delivery;

3.2 if sent by first class pre-paid post, 5 business days (Saturdays, Sundays and Bank or other public holidays excluded) after being placed in the post;

3.3 if sent by facsimile upon receipt of the faxed back first transmission page to confirm receipt

3.4 if by express mail or by courier within 2 days after being despatched.

AS WITNESS the hands of the duly authorised representatives of the parties hereto the day and year first before written.

SIGNED BY
For and in behalf of
CELLTECH THERAPEUTICS LIMITED .....

Title

SIGNED BY
For and on behalf of
IXSYS INC .....

Title

2. Supply of the Customer Materials

2.1 Prior to or immediately following the date of the Agreement the Customer shall supply to Celltech the information referred to in Clause 1 (i) of Schedule 2 hereto followed at the appropriate time by supply of the Customer Materials and Customer Information, together with full details of any hazards relating to the Customer Materials, their storage and use. Property in the Customer Materials supplied to Celltech shall remain vested in the Customer.

2.2 The Customer hereby grants Celltech the non-exclusive right to use the Customer Materials and the Customer Information for the purpose of the Agreement. Celltech hereby undertakes not to use the Customer Materials or the Cell Line containing the Customer Materials or the Customer Information (or any part thereof) for any other purpose.

2.3 Celltech shall :

2.3.1 be responsible for the safe keeping of the Customer Materials in its possession and shall at all times keep the Customer Materials secure and safe from loss and damage in such manner as Celltech shall in its sole discretion determine;

2.3.2 not part with possession of the Customer Materials or the Product, save for the purpose of tests at the Testing Laboratories.

2.3.3 procure that all Testing Laboratories are subject to obligations of confidence substantially in the form of those obligations of confidence imposed on Celltech under these Standard Terms and where relevant procure that such Testing Laboratories are subject to obligations to comply with GLP.

2.4 Celltech shall not be liable for any loss, damage, costs or expenses of any nature, whether direct or consequential, occasioned by the carrying out (in whole or in part) of tests or the failure to carry out tests by Testing Laboratories, provided that such liability is not a direct result of the negligence or wilful misconduct of Celltech or Celltech's employees and that Celltech shall inform Customer of the occurrence of such loss, damage, costs or expenses as soon as is reasonably possible .

2.5 The Customer warrants to Celltech that to the best of its knowledge and belief :

2.5.1 the Customer is and shall at all times throughout the duration of the Agreement remain entitled to supply the Customer Materials and Customer Information to Celltech; and

2.5.2 use by Celltech of the Customer Materials and the Customer Information for the purposes of the Services will not infringe any rights (including, without limitation, any intellectual or industrial property rights) vested in any third party save that subject to the above warranty Customer gives no warranty as to Celltech's entitlement to use gene expression and production technology associated with the Process.

2.6 The Customer undertakes to indemnify and to maintain Celltech promptly indemnified against any loss, damage, costs and expenses of any nature (including court costs and legal fees on a full indemnity basis), whether direct or consequential, and whether or not foreseeable or in the contemplation of Celltech or the Customer, that Celltech may suffer arising out of or incidental to any breach of the warranties given by the Customer under Clause 2.5 above.

2.7 The obligations of the Customer under this Clause 2 shall survive the termination for whatever reason of the Agreement in respect of matters arising during the term of or pursuant to this Agreement.

3. Provision of the Services

3.1 Celltech shall and where relevant shall procure that Celltech Biologics plc shall diligently carry out the Services as provided in Schedule 2 and shall keep Customer informed of the progress of the Services and shall use reasonable endeavours to achieve the estimated timescales set out therein.

3.2 Notwithstanding the provisions of Clause 3.1 the timescales set down for the performance of the Services (including without limitation the dates for production and delivery of Product) and the quantities of Product for delivery set out in Schedule 2 are estimated only. Time of performance of the Services, time of production and time of delivery shall not be of the essence of the Agreement.

3.3 The Customer shall not be entitled to cancel any unfulfilled part of the Services or to refuse to accept the Services on grounds of late performance, late delivery or failure to produce the estimated quantities of Product for delivery. Celltech shall not be liable for any loss, damage, costs or expenses of any nature, whether direct or consequential, occasioned by :

3.3.1 any delay in performance or delivery howsoever caused;

3.3.2 any failure to produce the estimated quantities of Product for delivery.

3.4 Celltech shall comply with all statutory, regulatory and similar legislative requirements from time to time applicable to the Services under the laws of England. If the Customer requests Celltech to comply with any foreign statutory, regulatory or similar legislative requirements Celltech shall use reasonable commercial endeavours to do so provided that :

3.4.1 the Customer shall be responsible for informing Celltech in writing of the precise foreign requirements which the Customer is requesting Celltech to observe; and